Sandia RESEARCH

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IT'S ALIVE

BIOSCIENCES

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Sandia National Laboratories

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To request additional copies or to subscribe, contact:
CTO Office
Sandia National Laboratories
P.O. Box 5800, MS 0351
Albuquerque, NM 87185-0351
Voice: (505) 284-7761
jchall@sandia.gov

www.sandia.gov

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Credits:

CTO Office: Robert W. Leland, Andrew McIlroy, Julie Hall

Internal, Digital & Executive Communications Manager: Valerie Smith

Editor:
Nancy Salem
(505) 844-2739, mnsalem@sandia.gov

Writing:
Patti Koning, Neal Singer, Stephanie Holinka, Heather Clark, Sue Major Holmes, Holly Larsen

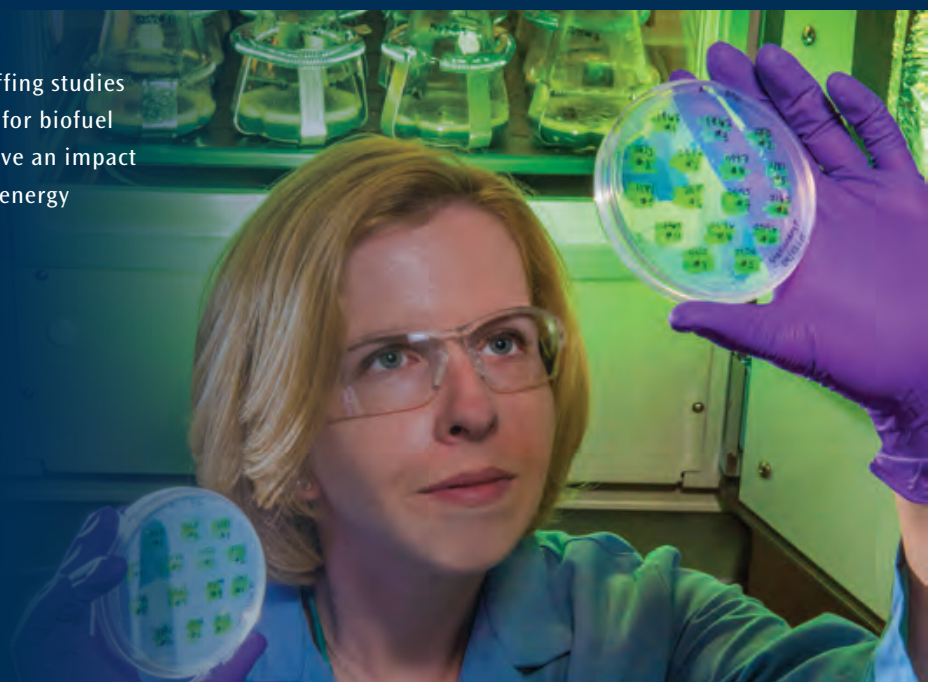
Photography:
Randy J. Montoya
Dino Vournas

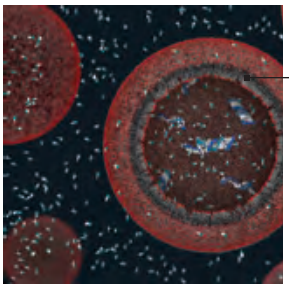
Design:
Michael Vittitow

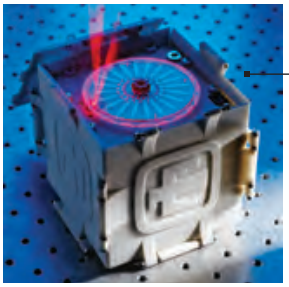
ON THE COVER

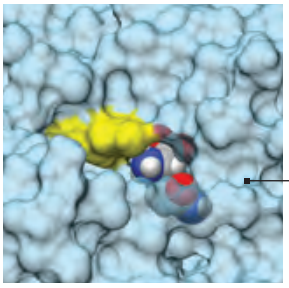
Sandia Labs engineer Anne Ruffing studies modification of cyanobacteria for biofuel production. "It's exciting to have an impact on an important problem like energy security," Ruffing says.

(Photo by Randy Montoya)









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Sandia RESEARCH

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Life UP CLOSE

The bioscience research program is relatively new in Sandia National Laboratories' 66-year history. While Sandia had pursued some biotech research since the 1980s, about 15 years ago lab leadership recognized the need for a more concerted effort in this area to address two national security risks: biological threats and U.S. reliance on fossil fuels.

Thus, bioscience became one of Sandia's research foundations, which are research areas considered key to the success of Sandia's national security programs. The goal of Sandia's bioscience work is to analyze, understand and control the functions of biological systems to meet national security challenges in biodefense, emerging infectious disease and energy security. For example, Sandia conducts research directed at helping defend against infectious disease outbreaks — such as the Ebola outbreak in West Africa — and bioterrorism, which have the potential to threaten human health, the economy and global security and stability.

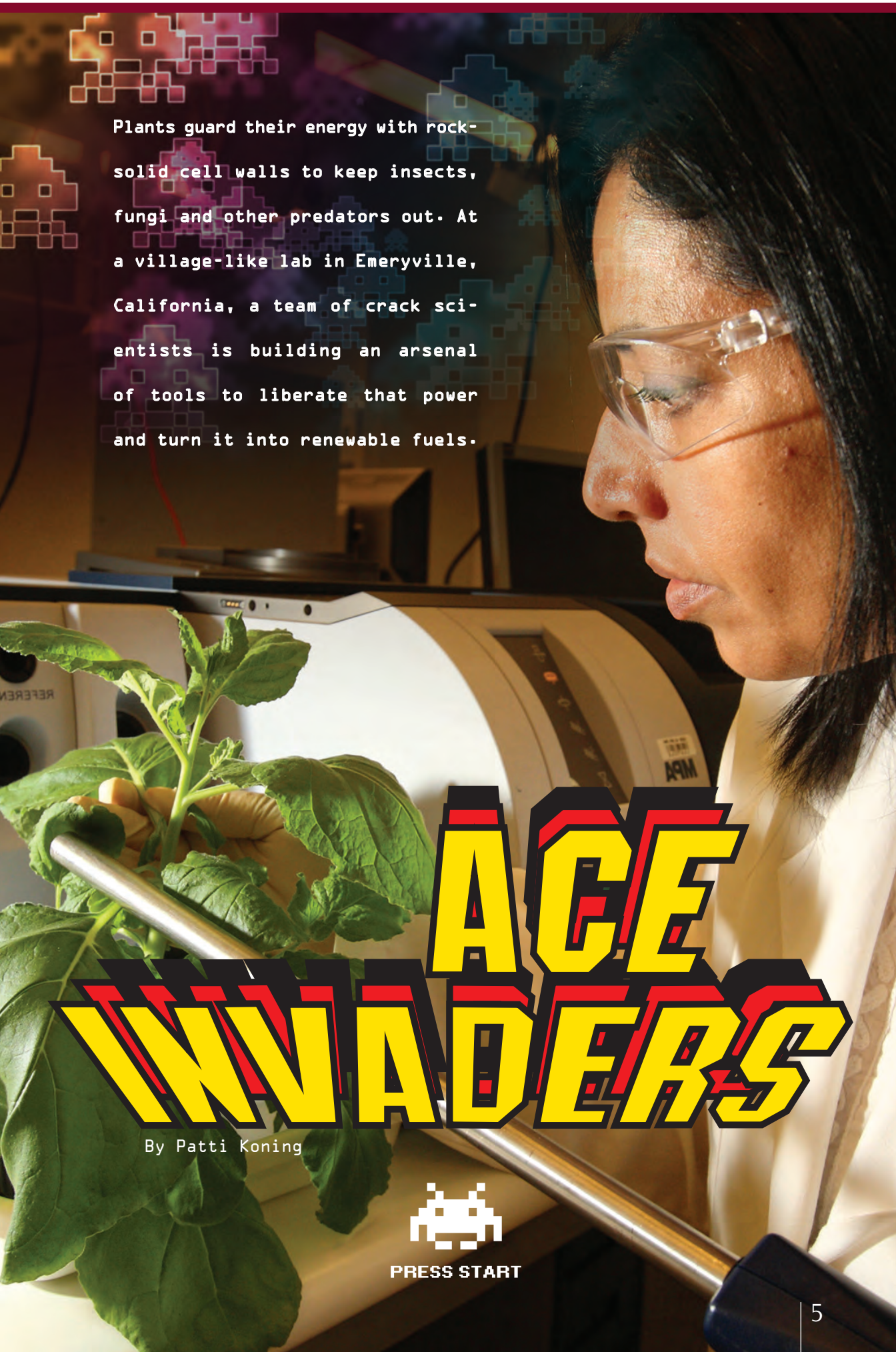
In its bioenergy program, Sandia's research focuses on efficiently, sustainably and economically generating renewable biofuels from lignocellulosic or algal biomass that show promise for displacing fossil fuels.

The stories in this issue of *Sandia Research* take a closer look at a number of Sandia's projects in biofuels, biodefense and emerging infectious diseases, including:

- Efforts to increase the efficiency of algae cultivation and harvesting so that algae can become an economically viable biofuel source
- A suite of Sandia projects directed at diagnosing and fighting the Ebola virus
- Work on "protocells," which could be used to deliver infectious disease-fighting medicine to specific targets within the human body
- Efforts of researchers at the Joint BioEnergy Institute to transform plant matter into biofuels
- Potential uses of SpinDx, a medical diagnostic lab-on-a-disk technology licensed by Sandia to several companies
- Work by Sandia microbiologists to understand how bacteria share genetic material and build resistance to antibiotics
- A treatment, developed jointly by Sandia, the University of Maryland and the MD Anderson Cancer Center, that could destroy a childhood cancer by starving it of a key nutrient

Finally, the issue includes a look back at µChemLab, Sandia's first Laboratory Directed Research and Development Grand Challenge. Nicknamed "chem lab on a chip," the compact device harnessed the power of a full chemistry laboratory to quickly detect and analyze bacteria, viruses and protozoa, spawning numerous related capabilities, patents and licenses, and even a few commercial products.

Malin Young
Director
Biological & Engineering Sciences



Plants guard their energy with rock-solid cell walls to keep insects, fungi and other predators out. At a village-like lab in Emeryville, California, a team of crack scientists is building an arsenal of tools to liberate that power and turn it into renewable fuels.

ACE INVADERS

By Patti Koning

PRESS START

Plants vs. scientists. That's one way to frame the Joint BioEnergy Institute's (JBEI) quest to transform dry plant matter, known as lignocellulosic biomass, into biofuels.

Lignocellulosic biomass is everywhere. The term describes what's left on the ground after harvest as well as grasses like switchgrass and miscanthus that grow naturally on marginal lands, requiring little water or fertilizer. Such grasses do not compete for resources with crops grown for food. Biofuels derived from this readily available biomass could provide clean, renewable, homegrown power for all of our country's cars, trucks and jet planes.

Over millions of years of evolution, plants have developed fortress-like cell walls to protect their energy, which takes the form of complex polysaccharide sugars. Lignin, the material that makes cell walls almost impervious, lets plants hold themselves upright, move water and protect themselves from predators. Plants can't run, so their defenses have to be rock solid.

Scientists, on the other hand, have been working on cellulosic biofuels for just a few decades. Even research into ethanol fuel, made from common crops like potatoes and corn, only goes back about 150 years.

To overcome this imbalance, JBEI researchers have amassed an impressive arsenal of tools and methods to liberate the energy stored in plants and transform it into renewable fuels and chemicals. These tools include "bionic" liquids, designer feedstock crops, microbial fuel factories, microbiology robots, engineered enzymes and filamentous fungi, just to name a few.

A higher level of science and technology

JBEI is like a self-sufficient village populated with diverse and richly experienced research scientists. A Department of Energy (DOE) Bioenergy Research Center founded in 2007, JBEI today has seven partner institutes: Sandia, Lawrence Berkeley National Laboratory, Lawrence Livermore National Laboratory, Pacific Northwest National Laboratory, the Carnegie Institute for Science and the Berkeley and Davis campuses of the University of California.

Blake Simmons, senior manager of Sandia's advanced biomanufacturing group and JBEI's chief science and technology officer, says that it's hard to overstate how ambitious JBEI's mission was back at the start.

"No one had done any of this before — focusing on the production of 'drop-in,' fungible biofuels realized through synthetic biology. Ionic-liquid pretreatment was a nascent field, and our Feedstocks group was taking a very different approach than had been tried previously," says Simmons. "These were deliberate choices on our part. We wanted to push the envelope and lift the entire biofuel enterprise to a different level of science and technology."

Creating biofuels from biomass was just the start. To be truly successful, those biofuels would need to be both compatible with existing infrastructure and engines and economically competitive with gasoline and other transportation fuels.

"What's crazy is that we weren't ambitious enough," he adds. "What we have accomplished in eight years blows away what we thought we could do when we started. In 2007, we simply could not imagine where we have ended up. And we aren't finished yet — not by a long shot."

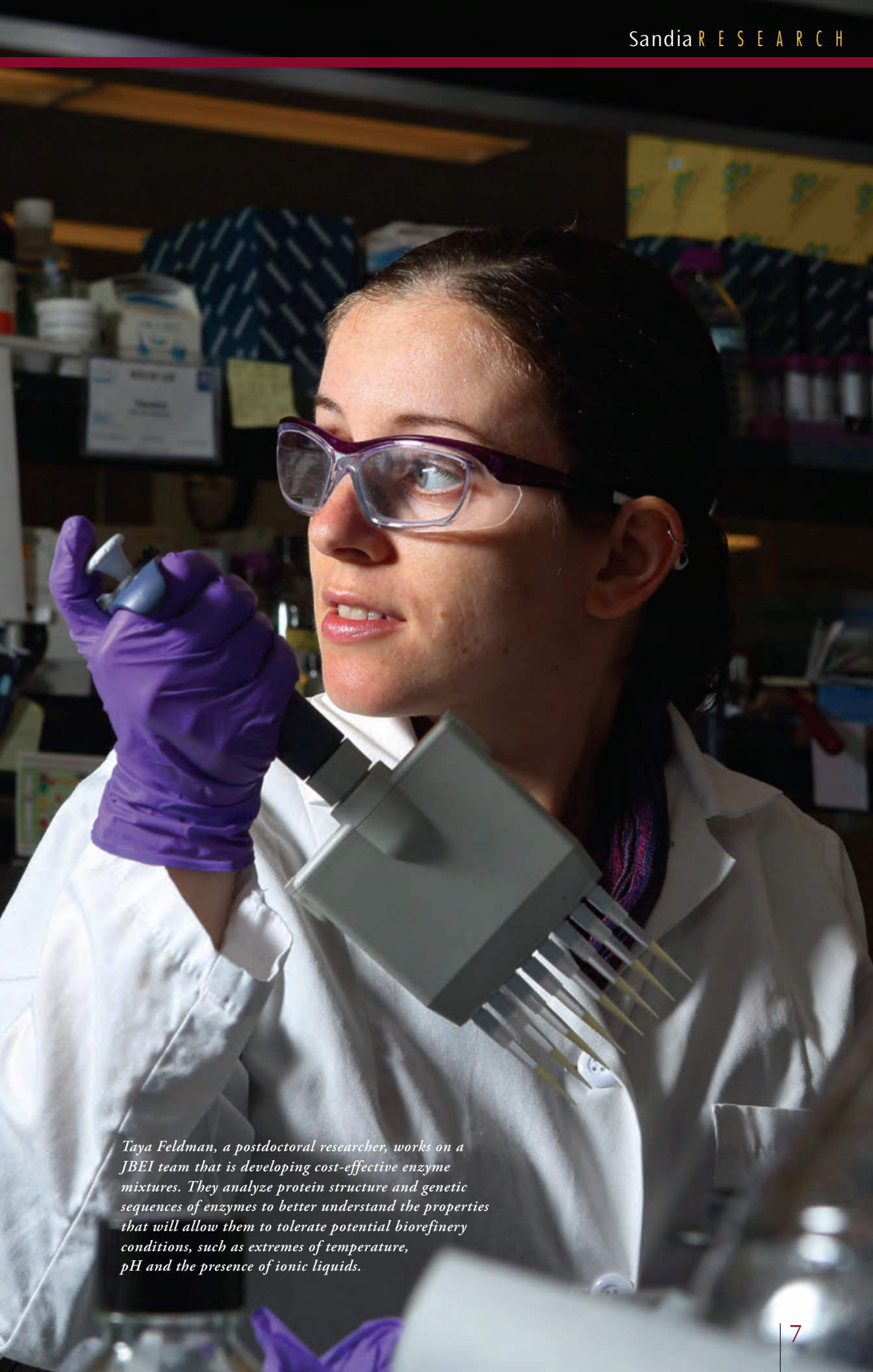
A sunlight-to-biofuels pipeline

In a departure from traditional research organizations, which typically focus deeply on a specific scientific challenge, JBEI brings the entire cellulosic biofuels production cycle together under one roof.

The institute is organized into divisions to match that cycle. Feedstocks breeds specialized fuel crops. Deconstruction seeks to release complex polysaccharide sugars from plant cell walls and reduce them to fermentable sugars. Fuels Synthesis engineers microbes to transform sugars into energy-rich biofuels, and the Technology division develops advanced analytical and software tools for all of JBEI.

Sandia researchers are concentrated in Deconstruction and Technology, with many directing key programs: John Gladden, Fungal Biotechnology; Ken Sale, Enzyme Optimization; Seema Singh, Biomass Pretreatment; and Anup Singh, Analytical Technology.

JBEI houses experts from many different research disciplines, including plant geneticists, biochemical engineers, chemists, physicists, microbiologists,



Taya Feldman, a postdoctoral researcher, works on a JBEI team that is developing cost-effective enzyme mixtures. They analyze protein structure and genetic sequences of enzymes to better understand the properties that will allow them to tolerate potential biorefinery conditions, such as extremes of temperature, pH and the presence of ionic liquids.

electrical engineers, microfluidicists and computer scientists. This gathering of diverse research expertise has accelerated JBEI's research program by uncovering unforeseen opportunities.

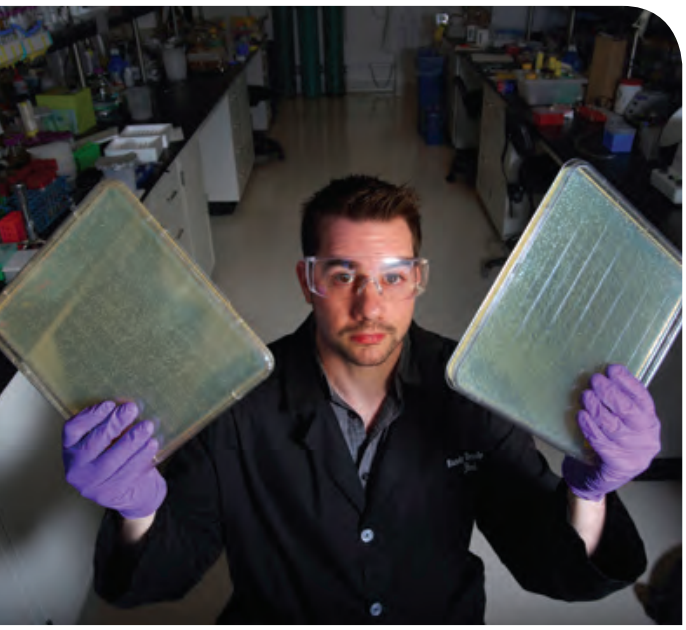
"Colocation created remarkable synergy between the teams," says Simmons. "When we wrote the original proposal, for instance, we intended to use synthetic biology for the Fuels Synthesis division only. But now the Feedstocks and Deconstruction divisions have incorporated synthetic biology into their programs. We are creating a synthetic biology platform that benefits all of JBEI that is cross-divisional."

Taming ionic liquids

Ionic liquids are one of JBEI's greatest success stories. Led by Seema Singh, JBEI researchers have been demolishing the arguments against using ionic liquids for biomass pretreatment.

"Ionic liquids effectively and efficiently dissolve biomass, but everyone said they were too expensive to be commercially viable," says Seema Singh. "The problem seemed impossible, but the best science can happen when your back is against the wall. We hit upon a novel idea to synthesize an ionic liquid from lignin and hemicellulose, which are byproducts of biorefinery production."

The result was "bionic" liquids, which matched the performance of imidazolium-based ionic liquids, the current gold standard for dissolving biomass. The next hurdle was compatibility with the enzymes that perform the next step in the deconstruction process.



JBEI's Randy Drevland holds plates of E. coli *used to evolve more stable enzymes for biofuel production.*

Imidazolium-based ionic liquids don't play well with the enzymes. In fact, some ionic liquids can be toxic to enzymes. Thus, costly and time-consuming washing steps are typically needed to remove ionic liquids from biomass before enzyme treatment can begin.

However, these steps could be eliminated if other JBEI teams succeed in their mission to find enzymes that are durable, heat-tolerant and uninhibited by ionic liquid. Discovering these enzymes is critical to the biomass-to-biofuel process.

With the desired characteristic set in mind, the Microbial Communities group searches for enzymes in unique ecosystems, such as rainforest floors, salt marshes and compost. Another dedicated team, the Enzyme Optimization group, seeks to design ideal enzymes through enzyme engineering — specifically, via a method called directed evolution.

Perfect enzymes through directed evolution

Directed evolution both mimics and accelerates natural selection by subjecting a gene to iterative rounds of mutagenesis. Researchers can then screen for desired characteristics.

There are thousands of potential enzymes, but this search takes the needle-in-a-haystack concept a step further. "More like looking for a needle in a haystack when you don't know what a needle looks like," says Sale. "We don't know what makes an enzyme functional in ionic liquid. And there is a lot of variety in ionic liquids."

A further complication is that the researchers aren't looking for a single enzyme. A cocktail of several enzymes is needed to completely convert the sugars that make up the polymers in plant cell walls into the monomeric sugars used by engineered fuel-synthesizing host organisms.

"The goal is to discover ionic-liquid-tolerant versions of these enzymes to build a minimal enzyme cocktail," says Sale. "Enzymes are expensive. They represent about a third of the total cost of converting biomass to biofuels, so anything we can do to drive down the cost matters."

MEET

Seema Singh

Seema Singh loves a challenge, the bigger the better. "I played basketball throughout high school and college," she says. "I'm not tall, so I was driven to become an even better player. I made up for my lack of height by becoming skilled at distance shooting. I also love how teamwork is essential to playing basketball well. Talent will only take you so far if you can't work with your teammates."

Singh feels she has come full circle working in biofuels. She remembers going to her grandfather's farm as a child and seeing the pride he took in growing food. "Perhaps post-retirement, I will have my own farm, growing bioenergy crops," she says.

One of the most exciting projects she has worked on at Sandia in recent years is bionic liquids. These are ionic liquids made from lignin and hemicellulose, two byproducts of biorefineries. Bionic liquids are nontoxic and much cheaper than petroleum-derived ionic liquids. Singh and her team are researching biocompatible bionic liquids that work with commercial enzymes cocktails and novel ionic liquids-based processes for lignin utilization.

STATS

- Bachelor of Science in chemistry and biology and Master of Science in organic polymer chemistry and drugs and antibiotics, UGKP, India
- Master of Science in physical chemistry and Ph.D. in physical chemistry/biophysics, University of New Mexico
- Expertise in biophysics, material science, interfacial science and biofuels, and in probe microscopies, novel single-cell imaging and spectroscopy techniques
- R&D 100 award for superhydrophobic coating, 2008
- Associate editor for *Frontiers in Energy Research, Bioenergy and Biofuels*
- Director, biomass pretreatment, and deputy vice president of the Deconstruction Division, Joint BioEnergy Institute
- Organizing Committee member, Symposium on Biotechnology for Fuels and Chemicals
- Adjunct faculty, University of Minnesota
- Editorial board, *Applied Biochemistry and Biotechnology*
- American Institute of Chemical Engineers chair for Advances in Biofuels: Department of Energy Bioenergy Research Centers

In addition to screening large numbers of enzymes, the team is working to engineer ionic-liquid tolerance into enzymes identified as good candidates. Using error-prone polymerase chain reaction (PCR) methods, the researchers make random mutations to the DNA that codes for the protein, grow thousands of different mutated versions of the proteins in *E. coli* and screen the mutated versions based on their activity in ionic liquids. Mutants with improved performance in ionic liquids are then subjected to additional rounds of random mutagenesis and screening to generate top performers.

E. coli is a good host for exploration. It grows quickly and is used broadly in the microbiology community, so there are many tools available for working with

Faces of JBEI, clockwise from left, Anthe George, Tanmoy Dutta, Jeemeng Lao and Benjamin Schwessinger

the bacteria. Unfortunately, *E. coli* is not reliable at producing larger quantities of enzymes.

The Fungal Biotechnology group, added in 2012, seeks to address this shortcoming by using the fungi *Aspergillus niger* as a genetic toolbox for more efficient protein production. The group's research focuses on expediting the discovery of high-performance, industrial-strength enzyme cocktails.

"Our goal is to understand how *A. niger* is able to express and secrete such high concentrations of enzymes so that we can manipulate this organism to produce our engineered ionic-liquid-tolerant enzymes inexpensively and at industrially relevant concentrations," Gladden says.

Biology on a chip

Creating and screening thousands of cells with conventional methods would be costly and time-consuming. However, Anup Singh's Analytical Technology group, which is part of JBEI's Technologies Division, is developing ways to accelerate and automate screening for a number of applications relevant to biofuels research. Using Sandia's microfluidics expertise, his team is developing an automated platform for "synthetic biology on a chip."

While engineering pathways in *E. coli* to produce chemicals, including biofuel molecules, has become routine, such research still requires many time-consuming and costly experiments. The Analytical Technology group's goal is to automate the entire process in a microfluidic chip. The team has proved the concept can work in an experimental setting with 10 assays running simultaneously. The next step is to scale up and eventually create an end-to-end device.

"We want to be able to program a desired pathway into a computer, which will identify the potential genes," says Anup Singh. "Then our device will synthesize the DNA, introduce it into *E. coli*, grow the *E. coli* cells and test whether the desired molecules are produced. This is the most ambitious project I have worked on in my career at Sandia. We might fail, but if we don't try, we will never succeed."

The same microfluidic technology also is being used for finding better enzymes and cocktails of enzymes. Rather than think too much about what mutants of enzymes to make, explains Anup Singh, "we use error-prone PCR to generate large libraries of mutants and then use our chip to screen for the ones that work the best. Our automated platform can also quickly screen for enzyme combinations with the best activity in ionic liquids and discard the ones that don't work."

Another reason to take on such an ambitious project is the commercial potential. "If we succeed, we hope to spin off a company," he says. "This type of inexpensive multiplexing has a lot of applications in human health."

Aiming for the marketplace

Spinning off companies, licensing technology and intellectual property (IP), and creating fruitful partnerships are all key markers of JBEI's success. All of

the technological advances wouldn't mean much if they couldn't be translated to the marketplace.

"We recognized early on that for our mission pull, just doing great science was not acceptable," says Simmons. "We had to do great science that was driven by the needs of the marketplace and of industry. The world was not just going to come to us. To succeed in the realm of biofuels and renewable energy, we'd have to engage with industry and work on the things that matter the most and that industry can't do."

As proof of the institute's success, Simmons points to the long list of JBEI patents, IP licenses and spin-off startup companies. "Roughly speaking, half of our technology disclosures turn into patents, and half of those have already been licensed," he says. "Those are astronomical numbers."

That success didn't happen by accident. As research programs were developed, the JBEI founders also built an industry partnership program and created a one-stop shop for IP and licensing. This means interested industry partners work with JBEI only, not the individual home institutions of the inventors.

Another key element is the Techno-Economic Modeling program, which is available to all JBEI researchers and the outside community at econ.jbei.org. "This team can set up a baseline biorefinery and run different scenarios — what would happen if we change the pretreatment process or establish a new biofuel production process — and find those intersections between our research and what really matters to industry," says Simmons.

Beyond bionic liquids

While basking in the success of her bionic liquids, Seema Singh received a reality check from an authority in the lignocellulosic biorefinery world. Although he praised the team's advances with bionic liquids, he urged them to reconsider their reliance on specialized enzymes and microbes that aren't commercially available.

"He said he'd love to implement our ionic-liquid-based methods to maximize sugar and fuel in an upcoming bioenergy plant if a commercial cocktail could be used," she says. "I realized that industry wants simple solutions and that companies are ready today if the economics make sense."

This drove Singh and her team to create a biocompatible bionic liquid that works with commercially available enzymes. For this task, they had to first overcome a pH mismatch between the pretreatment and hydrolysis processes when using basic biocompatible ionic liquids.

"We are currently exploring biocompatible ionic liquids that have pH levels between 8 and 14, but the hydrolysis process requires a pH level of about 6 to 7. Adding acid, a common way to lower pH, causes salt formation, which renders the bionic liquid unrecyclable," she explains.

With their backs against the wall again, the research team came up with another novel approach that may solve the pH mismatch. Those results will be published in 2015.

The next frontier, says Singh, is reducing the severity of the pretreatment process. Currently, pretreatment is conducted at temperatures of 120-160°C.

"We are screening for ionic liquids that work at lower temperatures and in the presence of water. We have found promising candidates that work at 70°C. That's good, but I think we can do better," she says. "By using designer solvents, I believe biomass pretreatment can be performed at room temperature. We are also striving for commercially viable and scalable one-pot pretreatment-conversion processes for biomass so that biofuels can replace the commodity fuels and chemicals made from a barrel of oil." GAME OVER

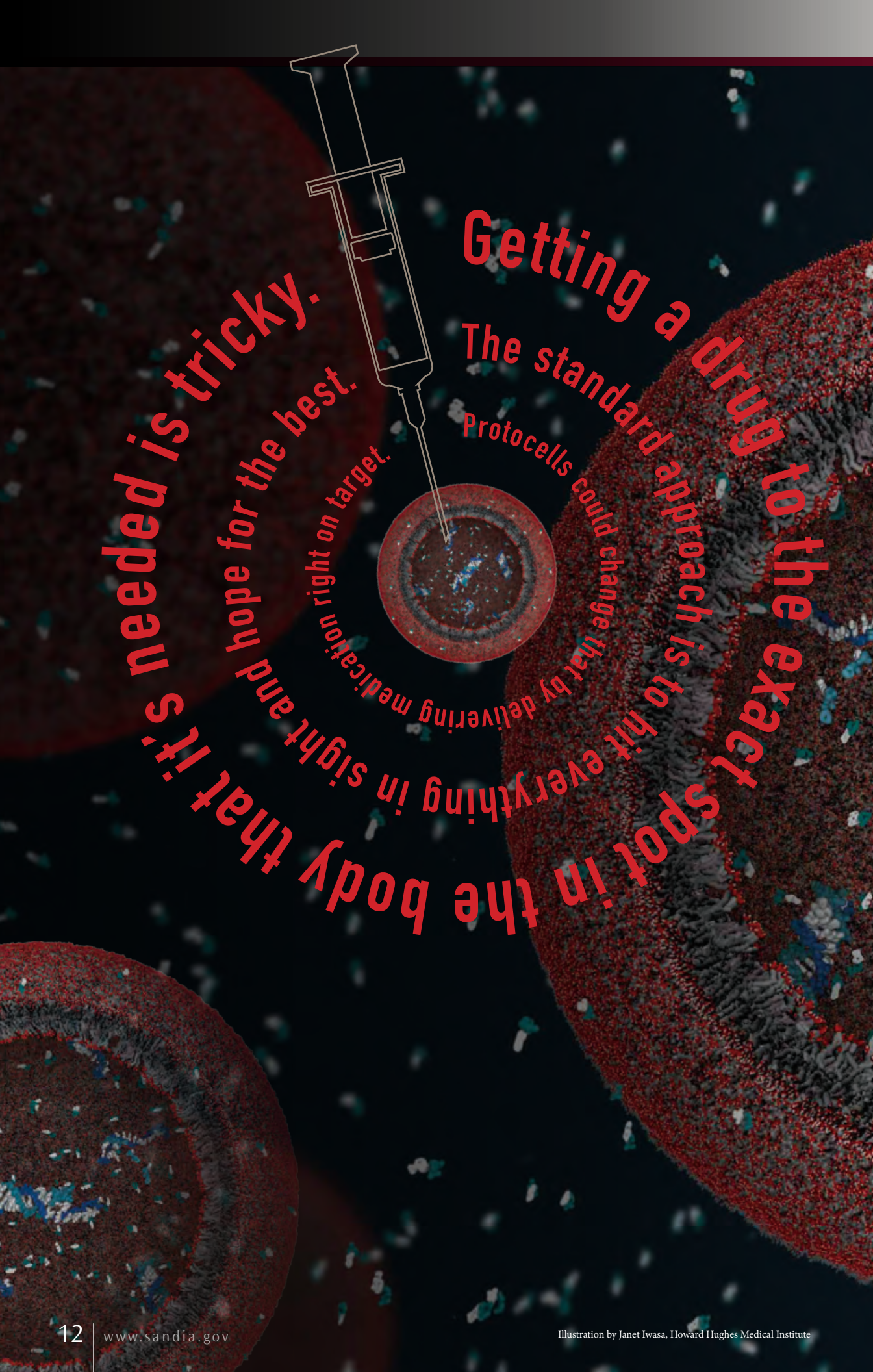
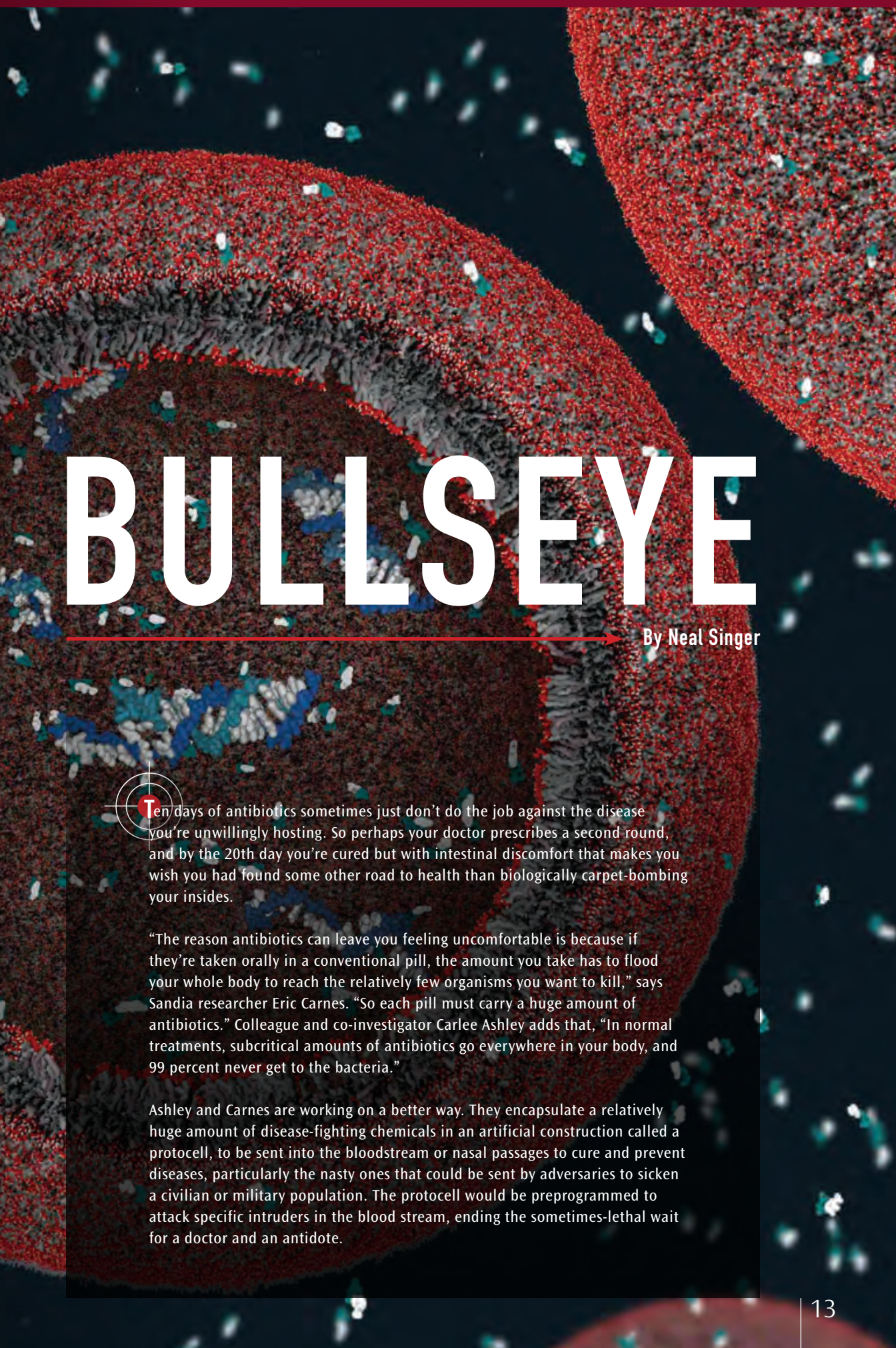


Illustration by Janet Iwasa, Howard Hughes Medical Institute



BULLSEYE

By Neal Singer

Ten days of antibiotics sometimes just don't do the job against the disease you're unwillingly hosting. So perhaps your doctor prescribes a second round, and by the 20th day you're cured but with intestinal discomfort that makes you wish you had found some other road to health than biologically carpet-bombing your insides.

"The reason antibiotics can leave you feeling uncomfortable is because if they're taken orally in a conventional pill, the amount you take has to flood your whole body to reach the relatively few organisms you want to kill," says Sandia researcher Eric Carnes. "So each pill must carry a huge amount of antibiotics." Colleague and co-investigator Carlee Ashley adds that, "In normal treatments, subcritical amounts of antibiotics go everywhere in your body, and 99 percent never get to the bacteria."

Ashley and Carnes are working on a better way. They encapsulate a relatively huge amount of disease-fighting chemicals in an artificial construction called a protocell, to be sent into the bloodstream or nasal passages to cure and prevent diseases, particularly the nasty ones that could be sent by adversaries to sicken a civilian or military population. The protocell would be preprogrammed to attack specific intruders in the blood stream, ending the sometimes-lethal wait for a doctor and an antidote.

A kaleidoscope of shapes

A protocell is pretty small — about 150 nanometers in diameter or less — and made from a surprisingly simple recipe. Imagine a molecule with one end that hates water and one that loves it. Put a bunch of them — usually surfactant molecules, similar to those in kitchen soaps — together in water and either spin or aerosolize them dry. The molecules arrange themselves, or self-assemble, into very tiny circles, spheres, carpets and cylinders, as orderly as a kaleidoscope might produce. The exterior of the structures are water-loving, hydrophilic molecules and the interior are hydrophobic molecules, hanging out about as far as they can get from water. The water-hating molecules are removed, either by heat or solvent extraction.

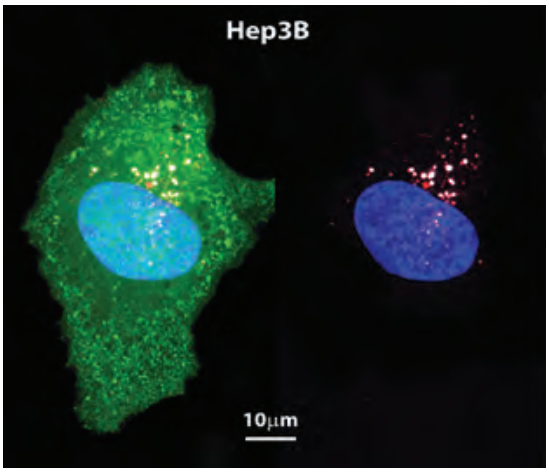
At the center of each tiny structure where the water-hating molecules had been are vacancies, re-rentable as possible storage areas. There are thousands of them in each protocell, which self-assemble from thousands of the substructures. The vacancies have this useful property: They act as sponges to suck up the medical materials in which Carnes and Ashley immerse them. This storage capability, unavailable in scope with any other method, makes protocells powerful vehicles to deliver medicine to internal sites, a kind of Death Star to invading bacteria or chemicals.

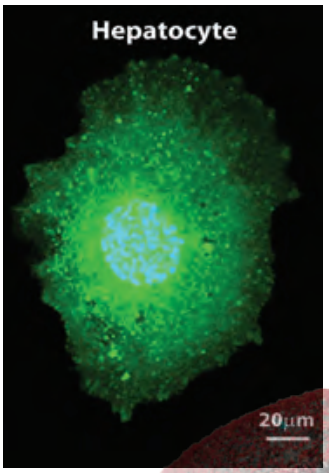
After saturating the nanosponges with medicines, Ashley and Carnes immerse large groups of the particles in a lipid solution — a grease identical to the membrane material that wraps all human cells. The lipids self-assemble into protective coatings, forming protocells, tiny structures with cell-like coatings that perform microscopic activities. These coatings not only help corral medicine within the protocells, they provide a surface that the body's immune system does not view as foreign. This allows the particles to stay in the bloodstream significantly longer than typical antibiotics, making more time available for the protocells to contact and destroy invading bacteria.

To the lipid coating of the protocells, researchers install small amounts of targeting ligands, small proteins that bind like a grappling hook to a targeted cell. "When we're going after viral infections, we know how viruses enter cells, so we copy whatever the virus is ready to bind to. In effect, we use the same broken window the virus created to enter the attacked cell," says Carnes. "Our protocells don't get attacked by the immune system because while viruses have a high

Above, researcher Carlee Ashley works with Sandia Fellow and University of New Mexico professor Jeff Brinker to add a buffer to dilute a protocell.

The Hep3B image below shows a cancerous liver cell penetrated by protocells. The small red dots are lipid bilayer wrappings carrying drug-filled nanoparticles, their pores filled with white fluorescent dyes for imaging purposes. A normal cell in the hepatocyte image shows no penetration.





MEET

Carlee Ashley

Carlee Ashley loves animals and wanted to do more to help than her long-standing monthly donations to the ASPCA. So she and her husband started fostering for Animal Humane New Mexico. They find it rewarding to have fostered dozens of puppies and kittens too young to be spayed or neutered and put up for adoption, as well as adult animals that need extra socializing or time to recover from an infection or surgery.

Ashley says her most rewarding scientific pursuit yielded protocell technology. It began in 2008 as part of a National Cancer Institute-funded Nanomedicine Development Center project to develop nanoparticle delivery vehicles for improved cancer diagnosis and therapy. She worked with Sandia Fellow Jeff Brinker and researcher Eric Carnes in collaboration with the University of New Mexico Cancer Center. The team developed protocells and demonstrated they are a million-fold more effective at treating drug-resistant cancers than liposomes and other state-of-the-art nanoparticles. "Developing protocells and showing they have the potential to more effectively treat cancer while also reducing the side effects of chemotherapy was especially rewarding because cancer is a disease that affects, either directly or tangentially, most people," Ashley says. "It's satisfying to know that something I helped create has the potential to save lives."

STATS

- Bachelor of Science in biochemistry and molecular biology, University of New Mexico
- Ph.D. in chemical engineering with a concentration in nanoscience and microsystems, UNM
- Won a $25,000 first-place award at the UNM Business Plan Competition
- Harry S. Truman Fellow
- First or corresponding author of four manuscripts featured on the covers of the journals *Nature Materials, ACS Nano, Advanced Healthcare Materials, 2011-2012*

density of protein antigens that serve as binding hooks, ours have few, shaped to attach only to receptors of the organism we want to kill. So we need to insert far fewer carriers and far less antibiotics in sum, because ours only go where they're designed to go."

Regain control over antibiotic resistors

The method, which the researchers have explored with research teams from UCLA, Georgetown, Duke and the universities of Oklahoma, Washington and North Carolina, is expected to be useful to people looking for less invasive ways to fight infections. The protocells' relatively large (because porous) carrying capabilities also could help reestablish medical control over diseases like MRSA that have developed resistance to conventional amounts of antibiotics.

And the protocells could act as an immunizer and antidote against chemical and biological attacks, fashioned to bind to particular arrangements of molecules known to host specific attackers.

Protocells themselves were the outcome of years of research by a team led by Jeff Brinker, Sandia Fellow and University of New Mexico Distinguished Professor, who mentored Ashley and Carnes. The first ones, made of silica and about 150 nanometers in diameter, were a natural for the fight against cancer.

That method has been licensed to a West Coast drug company through UNM's Cancer Center.

"However, to test the effect of protocells against infectious diseases — a true Sandia goal as a defense laboratory — the spin-dry method took too long to accumulate particles for our needs," Ashley says. "We needed not only to shift the size of particle distribution but produce many more of them. Just upgrading from testing mice to testing rats is a volume issue that requires five times more protocells."

Testing people, she says, would require several orders of magnitude more protocells. "So we went from evaporation-induced self-assembly to aerosol-induced self-assembly. We used nebulizers five feet long and we set up 10 of them."

This elevated them from producing 0.1 grams every three weeks of precisely sized protocells for cancer research to 100 grams a day of less precisely sized but eminently usable protocells for a variety of defense purposes. "We're focusing on massively scaling up for use on humans," she says. "We have all the cell data for the project showing it would work. We've shown we can deliver antibiotics to host mammalian immune cells infected by different microbes. We've shown we can cure the problem in a dish."

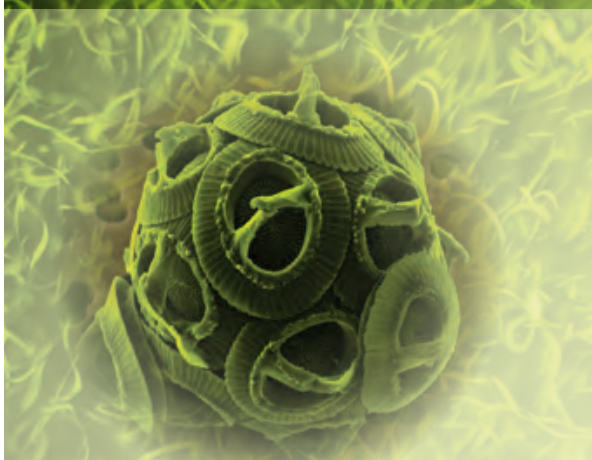
Full-scale tests coming up

The problem for the researchers is that they can do a safety study on humans to make sure using protocells does no harm, but not full-scale tests of their efficacy until such testing is approved by the U.S. Food and Drug Administration.

The Department of Defense is funding the project at $12 million over four years and seems willing to wait. "We're typically among the teams awarded projects in chemical defense and biodefense," says Ashley. "We use protocells to deliver nucleic acids that prevent viral and bacterial infections by targeting the pathogen's genome to prevent it from replicating. We can use it as a pretreatment to put in the blood, ready to respond if a pathogen is released. It's a new concept that will be very powerful down the line, but those types of therapeutics require more development."

Meanwhile, she says, "We can easily adapt protocells to absorb compounds like antibiotics, antivirals, vaccines, nerve agent countermeasures and protein RNA and DNA." ■

what's next



RACE IS ON TO EXPLORE THE HEART of ALGAE

You can grow algae without even trying. Leave your dog's water dish outside or forget to add chlorine to the swimming pool and in a week or two you'll have a nice algal bloom.

That makes algae one of the most promising long-term, sustainable sources of biomass and oils for fuel, food, feed and other products. But algae can disappear as quickly as it appears, in a phenomenon known in the biofuels industry as "pond crashes."

"Algae are at the bottom of the food chain, so they are susceptible to infection and predation from many different sources," says Sandia researcher Ryan Davis. "Combating this, along with improving the efficiency of harvesting methods, are among the biggest hurdles

Electron micrograph image by NEON ja, colored by Richard Bartz

By Patti Koning

to overcome before algae are an economically viable source for biofuel."

Sandia pioneered real-time monitoring of algae cultivation systems and early detection of algae pathogenesis and predation. Using pathogen detection and characterization technologies developed in the Rapid Threat Organism Recognition (RapTOR) project led by Todd Lane and adapting the SpinDx diagnostic tool for algal ponds, researchers created "PondDx," a rapid nucleic acid hybridization-based detector along with other tools.

Researchers also drew on advances in pretreatment and conversion methods made by their Joint BioEnergy Institute (JBEI) colleagues. While JBEI's mission is to convert into biofuels lignocellulosic biomass — non-food plant fiber that is tougher to break down than algae — their findings on ionic liquids and enzymes were useful to the algae researchers.

In the summer of 2015, Sandia will begin growing, monitoring, testing and cultivating algae at its Livermore, California, site in a testbed made up of three 1,000-liter raceways. Researchers previously used testbeds through the Algal Testbed Public Private Partnership (ATP3). Sandia is an ATP3 partner with several researchers in leadership roles.

"This will unify many disparate projects and capabilities around algae research. We have people working on processing, diagnostics, modeling and harvesting," Davis says.

Ron Pate is leading a project to develop an alternative approach to algae cultivation using a "turf scrubber" to increase the efficiency of cultivation by removing nutrients from wastewater. This system uses a narrow flow way to grow natural assemblages of macroalgae in a dense mat that is easier to harvest.

Researchers also are investigating ways to integrate processing steps. One promising method would combine hydrothermal and biochemical processing to boost efficiency while removing many of the contaminants that plague downstream processing.

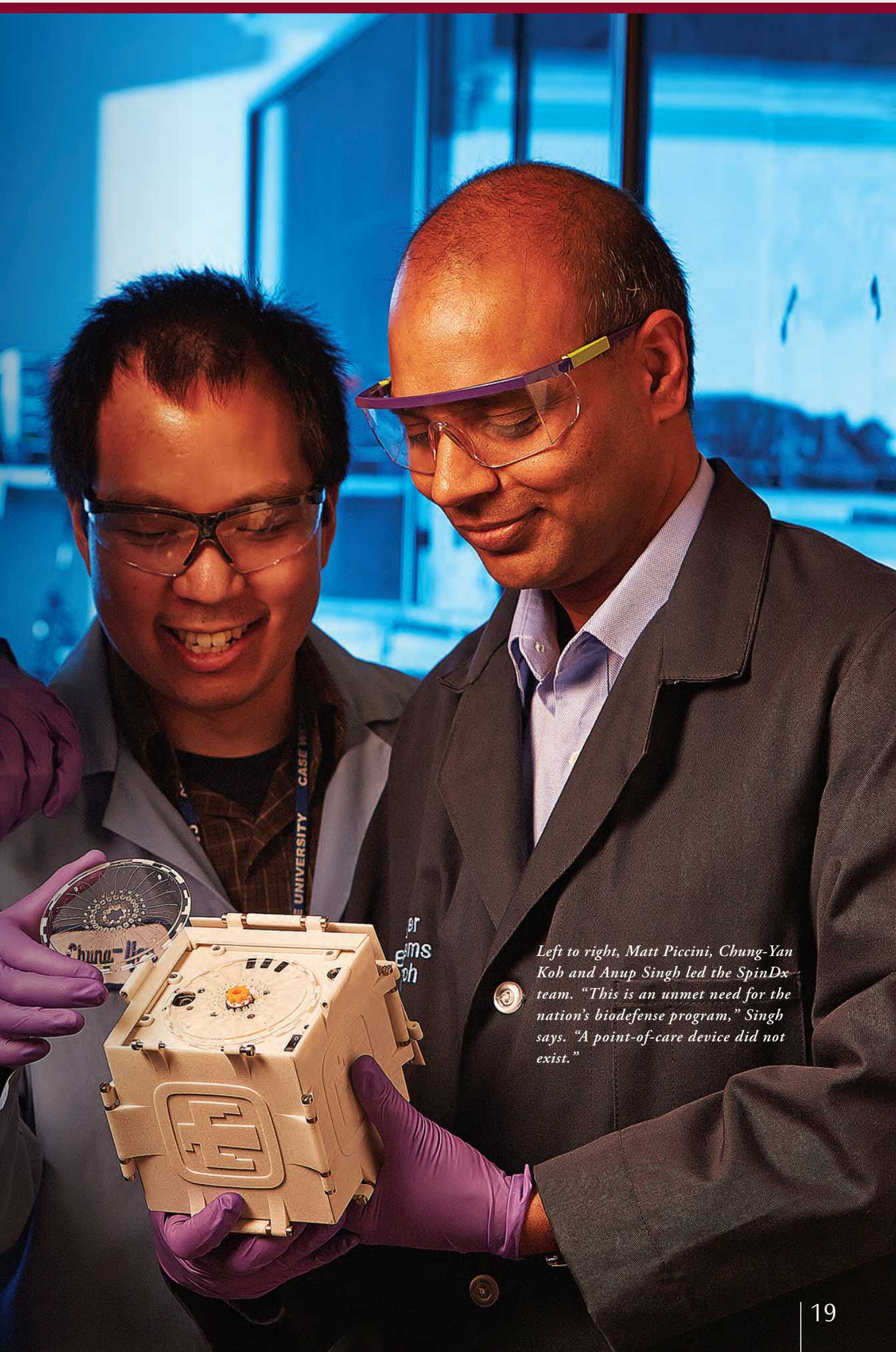
The testbed is indoors in an environment stringently controlled for light and temperature, but open biologically. "The first step is to move our existing benchtop algae cultivation programs to the indoor raceways," says Davis. "Eventually, we hope to have a parallel outdoor system. We need to test how our methods hold up in industrial cultivation environments."

The algal raceway testbed is strategically located at the Livermore Valley Open Campus, a space for open collaborative work that spans the border between Sandia's Livermore site and Lawrence Livermore National Laboratory. ■

Todd Lane, left, and Ryan Davis are leading efforts to better understand the large and diverse group of organisms known as algae.

IT LOOKS LIKE A BLOCKY CD PLAYER, BUT AS SPINDX WHIRLS IT REVEALS VITAL HEALTH INFORMATION — WHEN SECONDS COUNT.....

BY STEPHANIE HOLINKA



Left to right, Matt Piccini, Chung-Yan Koh and Anup Singh led the SpinDx team. "This is an unmet need for the nation's biodefense program," Singh says. "A point-of-care device did not exist."

Sometimes doctors, patients and first responders need answers fast to save lives. They can get them from Sandia's lab on a disk, SpinDx, which quickly identifies risks from disease, chemical and biological attack and contamination.

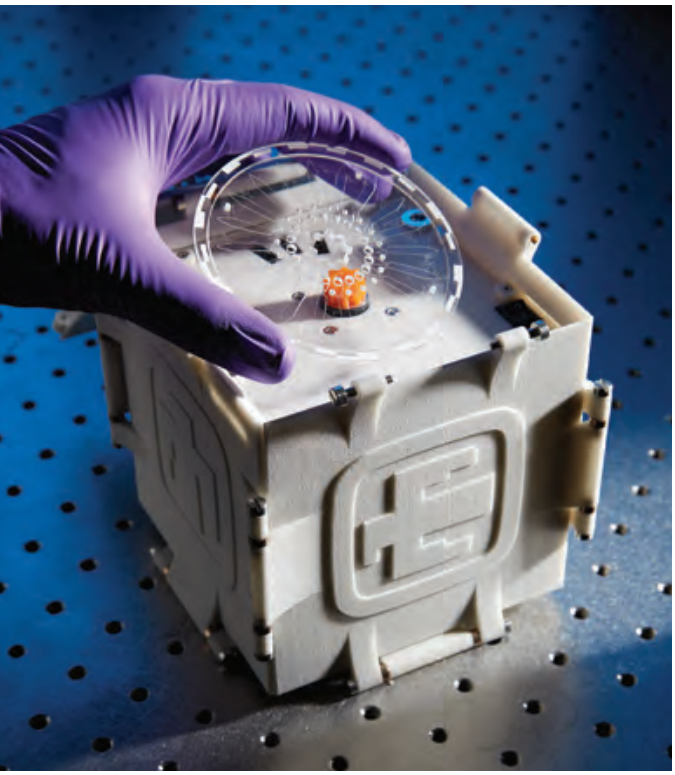
SpinDx works much like a CD player. A disposable plastic disk containing test reagents spins around in the device to manipulate an extremely small liquid sample, generating results within 15 minutes. The disks cost mere cents to manufacture, and different disks can be used in a single device to test for different concerns.

Four industry partners have licensed and are commercializing the technology.

Answers in the doctor's office

The impact on patient care could be profound. "In a doctor's office, SpinDx would allow for quick diagnoses of many illnesses normally diagnosed using tests that can take days or weeks to come back from a laboratory," says Anup Singh, senior manager in Sandia's Applied Biosciences & Engineering group.

He says SpinDx can determine a patient's white blood cell count, analyze important protein markers and process up to 64 assays from a single sample, all in a matter of minutes. It could be used in cardiac health, cancer and infections such as HIV or hepatitis where lab-based tests are the norm. "Heart attacks, strokes, infections, certain cancers and other afflictions could be detected days or weeks sooner than they are today with no new burdens placed on patients or their doctors," Singh says.



Instead of standard blood panels and costly lab tests, a SpinDx disk would process a sample right in the office in the time medical staff would take to gather routine data like temperature and blood pressure. "Disks can be developed that test for suites of illnesses that share similar symptoms such as West Nile virus, chikungunya and dengue fever," Singh says. "This could allow health care workers to rule out dangerous diseases that could prompt quarantine or other protective measures."

Licensee Sandstone Diagnostics in Livermore, California, plans to launch a pipeline of medical testing products, starting with simple home test kits and expanding into broader areas of health care. Its male fertility test kit for consumers will begin FDA trials soon. Sandstone expects to bring the product to market by early 2016. The company also has two ongoing National Institutes of Health-funded projects investigating point-of-care diagnostic devices for rapid neonatal sepsis monitoring and for ultra-sensitive biotoxin diagnostics.

Lifeloc Technologies Inc. of Wheat Ridge, Colorado, is working with Sandia under a cooperative research and development agreement to develop assays that test for drugs commonly abused by addicts.

And licensee POC Medical Systems Inc. of Livermore, California, is developing disks that will test for cardiac and breast cancer. The breast cancer test is nearing commercialization; a single drop of blood is enough to test with 90 percent accuracy for the set of biomarkers that are relevant for the disease. The test costs $2 and will be introduced in India and then Europe and China.

Finding contamination in food and water

SpinDx's ability to process many substances makes it suited to food safety testing. About 15 percent of botulism cases are foodborne. In 2007, 14 people in seven states contracted the potentially fatal illness from chili sauce tainted by faulty manufacturing equipment at a food plant in Georgia. The disk can handle thick, viscous food substances. Testing collaborators at the U.S. Department of Agriculture

MEET

Chung-Yan Koh

Chung-Yan Koh is a musician at heart. He has a degree in piano performance and once played cello with the Cleveland Orchestra at the Blossom Music Festival during its summer season. "Having grown up listening to their recordings, it was incredibly intimidating going into the audition process, but everyone was very kind during the entire event," he says. "The summer festival tends to be more light-hearted than the regular season."

At Sandia, materials Chung-Yan and other graduate students developed while he was working on his thesis led to one of the first demonstrations of successful engraftment and functional revascularization of transplanted Islets of Langerhans. "It was the first time I was involved in translational research, and it sparked my interest outside of academic science," he says.

He is currently leading the development of portable microfluidic biodetection systems such as SpinDx. "As recent events have demonstrated, the ability to rapidly and accurately differentiate between pathogens which may have similar clinical symptoms is vital. Lab-on-a-chip platforms like SpinDx are able to automate and miniaturize complex, time-consuming fluidic manipulations yielding a device that is faster, cheaper, smaller and easier to use," he says.

STATS

- Bachelor of Science in biomedical engineering, Case Western Reserve University
- Master of Science in macromolecular science and engineering, Case Western Reserve
- Bachelor of Music, piano performance, Cleveland Institute of Music
- Ph.D. in chemistry, Northwestern University, Evanston, Illinois. His dissertation research was on design and synthesis of self-assembled nanomaterials as vehicles for targeted drug delivery, tissue engineering and regenerative medicine.

provided high-quality botulinum antibodies that bind well, enabling higher sensitivity.

Sandia also has a Laboratory Directed Research and Development project evaluating SpinDx for disease surveillance in animals used for food. Co-principal investigators Melissa Finley and Chung-Yan Koh are working in cooperation with Kansas State University, a school with a robust agricultural program.

Another market could be food processing plants to screen for food pathogens and toxins. "They need something that can be integrated into their assembly lines," Singh says. "SpinDx is fast, inexpensive and simple to operate."

SpinDx carts help public health workers determine whether food or water has been contaminated with toxins, viruses or bacteria. Licensee Safe-h2o Inc. of San Francisco uses the technology in its products that offer rapid detection of water-borne pathogens. The company intends to offer portable and lab-based units on the market along with assays that will test for top-tier waterborne pathogens such as *Cryptosporidium*, *Giardia*, *Legionella*, and *E. coli*. (Continued on page 23)

SCAN TO SEE VIDEO

SuperBAD

Sandia's BaDx anthrax detection cartridge has caught the world's attention. It won an R&D 100 award, and researchers Melissa Finley, Thayne Edwards and Jason Harper picked up the 2015 Federal Laboratory Consortium's Award for Excellence in Technology Transfer.

Bacillus anthracis, the bacteria that causes anthrax, is commonly found in soils all over the world and can cause serious, often fatal, illness in humans and animals. The bacteria can survive in harsh conditions for decades. In humans, exposure to *B. anthracis* may occur through skin contact, inhalation of spores or eating contaminated meat.

Sandia scientists, from left, Jason Harper, Melissa Finley and Thayne Edwards developed the BaDx anthrax detector.

Currently, samples for testing must be propagated in a laboratory that uses specialized tools requiring a consistent power supply, something often unavailable in the developing world, said Finley, who helps veterinary labs in less-developed countries improve safety, security and efficiency at diagnosing infectious diseases. "Working with dangerous samples like *B. anthracis* spores places laboratory staff at risk," she said. "Concentrating many positive test samples in a lab could also tempt someone to steal positive anthrax samples for nefarious uses."

BaDx is the size of a credit card and requires no battery or electric power to operate. It's hardy against wide temperature variation and can detect very small numbers of *B. anthracis* spores. That could make it especially useful in parts of the world where anthrax is prevalent, but refrigeration and lab facilities are lacking.

A field technician puts a sample swab into the amplification chamber, which contains selective growth media. The device then uses a lateral flow assay, similar to a common pregnancy test, to detect *B. anthracis.* Magnetically operated valves allow the sample to advance from stage to stage to complete the testing process. A colored line appears on the device several hours later, if the test is positive for the bacteria.

After testing, the technician can sterilize the device, which avoids the risk of positive samples accumulating and falling into the wrong hands. In addition to the sterilization process, the device is sealed closed, making extraction of live bacteria difficult.

Sandia has licensed BaDx to Aquila, a New Mexico small business that specializes in the design and manufacture of technologies and services for nuclear security and international safeguards. "We see a lot of potential for government customers and nongovernmental organizations as well as commercial markets," says company's chief scientist Markku Koskelo. ■

— Stephanie Holinka

Thwart bioterror threats

Biological attacks may not happen frequently, but they are deadly. In 2001, a week after 9/11, letters containing anthrax spores were mailed to several news media offices and two U.S. senators, killing five people and infecting 17 others. “Bio-attacks can impact the entire U.S. mail system and our government. These disruptive attacks have a social cost, a political cost and an economic cost,” says Singh.

SpinDx could allow a first responder to test in the field for a wide suite of biothreats including ricin, chikungunya, botulinum and Staphylococcal enterotoxin B toxin from just a single drop of blood or tiny amounts of white powder samples. “Ordinary testing for toxic substances is costly, can take days and requires highly skilled personnel,” says Singh.

Several Sandia projects are underway. The biggest project involves developing biodefense applications for the National Institutes of Health. Sandia has partnered with the University of Texas Medical Branch in Galveston, a premiere bio laboratory research center. “UTMB provides expertise and samples for markers of anthrax infection and in many ways is the ideal partner for this work. They have the types of labs that make testing and validating devices such as these possible and, ultimately, they’ll be customers for the device, so their engagement and feedback, especially in these early phases, is vitally important,” Koh says. “We’re doing some initial testing to see how easy it is for users to go through the process of sample testing and what changes need to be made to enhance usability, such as ergonomic or software changes.” UTMB is also helping to develop assays that can test five to 10 biotoxins against bioagents.

Another project is funded by the Department of Homeland Security to evaluate whether SpinDx can be used to test white powder samples. The goal is to develop a robust panel of tests that can be deployed at the point of incident (e.g., a mail room). By testing for several likely candidates at once, it is possible to rule in or rule out the presence of an agent and rapidly assess risk to personnel.

“Often, white powders that are suspected bioagents are really harmless substances such as sugar or coffee creamer,” Singh says. “But testing them is slow and expensive, and the decisions on whether to quarantine exposed people and potentially contaminated buildings can have huge financial and social costs.” Powdered samples can be dissolved in solution and tested against bioagents or suites of agents, and SpinDx will report a concentration level for a specific agent.

A smaller, internal project studies SpinDx as a platform for Ebola detection. “Currently there are a few FDA-approved Ebola tests, but they need to be performed in a lab,” Singh says. “Taking the test to the potentially infected people or location is safer than getting samples and transporting potentially infected people or samples to the lab.” ■

Greg Sommer co-founded the startup Sandstone Diagnostics. The Livermore, California, company licensed Sandia's SpinDx technology, which Sommer helped invent when he worked at the labs. Sandstone is developing commercial diagnostics instrumentation for clinical and life science research markets.

what's next

By Heather Clark

PUTTING THE **BRAKES** ON ebola

When Liberians suspect they have the deadly Ebola virus, they check into large, open waiting rooms called Ebola treatment units. Their blood is drawn and they wait to learn their fate. Patients with less serious illnesses are there, too, and risk catching Ebola and worsening an epidemic that has claimed more than 10,000 lives.

To cut that wait time and potentially fatal exposure, Sandia Labs has modeled and analyzed how blood samples in the West African nation travel from treatment units to diagnostic labs, and recommended a nationwide sample delivery system.

Sandia has other projects focused on fighting Ebola. They include developing a portable and inexpensive diagnostic tool, improving Africa's public health system and modeling an Ebola outbreak contingency plan for the U.S. Department of Veterans Affairs.

In Liberia, Sandia's sample delivery system is being adopted by the Liberian Ministry of Health, says Jen Gaudioso, manager of the labs' International Biological and Chemical Threat Reduction program. "Prior to our analysis, samples were being transported from treatment units to labs on an ad hoc basis," she says. "We developed a system, and the country is implementing our system."

In Sierra Leone, a Sandia employee is a coordinator for a diagnostic lab staffed by contractors who will help integrate it into the Ebola response system under the leadership of the country's Ministry of Health, Gaudioso says. Both Africa projects are sponsored by the Defense Threat Reduction Agency and United States Command Center for Combating Weapons of Mass Destruction.

Sandia will work to build a lasting public health capacity in West Africa. "As Ebola rates decline, you work with sustainability," says complexity scientist Tom Moore. "You don't want a permanent military presence addressing medical problems in Liberia." For example, Sandia's modeling could address resupplying medical equipment using models of Liberia's transportation infrastructure, says Pat Finley, who led the computer modeling effort in Liberia.

Sandia's models also are performing a systems level analysis to help develop contingency plans for treating Ebola patients in Veterans Affairs hospitals. The model, which could be applied to any pathogen, enables rapid analysis of the tradeoffs decision-makers would face, for example, the effects of setting up a pre-emergency room triage or a surge in influenza patients during an Ebola epidemic, Finley says.

And new research is using Sandia's lab-on-a-disk SpinDx platform to develop two methods to diagnose Ebola, says Anup Singh, senior manager of Applied Biosciences & Engineering. Researchers hope to develop one method to detect human response markers while the other will look for the Ebola virus by detecting nucleic acids in a pinprick volume of blood.

If successful, SpinDx could be used door to door and would be roughly 10 times cheaper than current laboratory tests. "It's early stage," Singh says, "but it looks promising." ■

MEET

Jeri Timlin

Jeri Timlin was a nationally and internationally ranked competitive baton twirler before going into science. She says the sport and long hours of practice helped her develop many of the attributes important to research, including strong organization skills, perseverance and creativity. She retired from twirling to start graduate school, but still enjoys the competitive track with occasional coaching.

Timlin works at the interface of chemistry, physics and biology and across scales from single proteins to communities. Her research focuses on developing and using advanced spectroscopic and imaging technologies to unravel spatial-temporal linkages in complex biological systems. "My strong engineering background definitely comes in handy," she says.

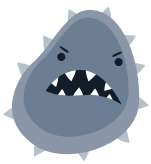
The research applications of her work are diverse and span the biofuels and biodefense missions at Sandia. In a recently completed biodefense project, Timlin worked with colleagues to develop multicolor optical super-resolution technology to characterize the earliest immune response to bacterial pathogens.

A three-year Laboratory Directed Research and Development program called the Benchtop to Raceway led to several peer-reviewed publications and many follow-up projects.

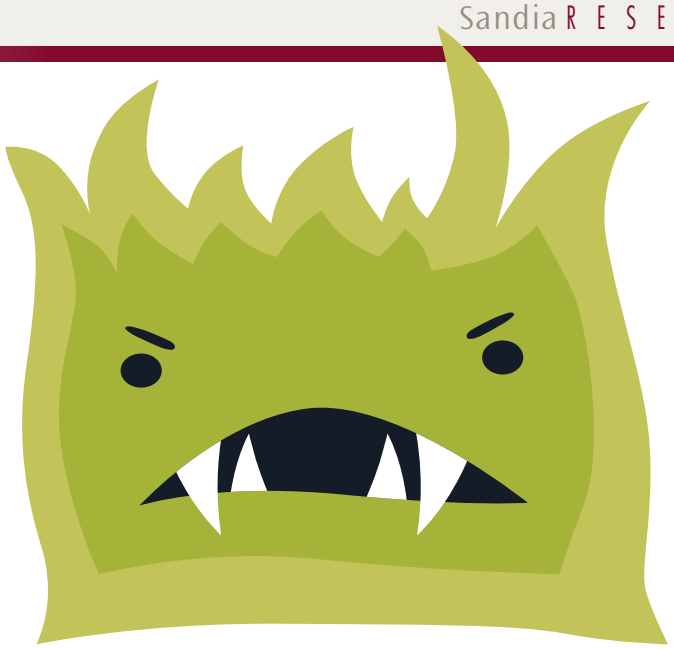
STATS

- Bachelor of Science in chemistry and chemical engineering with a minor in art, Geneva College, Beaver Falls, Pennsylvania
- Ph.D. in analytical chemistry from the University of Michigan
- Winner of the National Institutes of Health New Innovator Award, R&D 100 Award for "Hyperspectral Confocal Microscope," and Outstanding Women at Sandia National Laboratories

ANATOMY



Gene sharing helps bacteria build resistance to antibiotics. Understanding how that happens could yield new ways to bypass defenses.



OF A BUG

To fight a pathogen, first understand how it works.

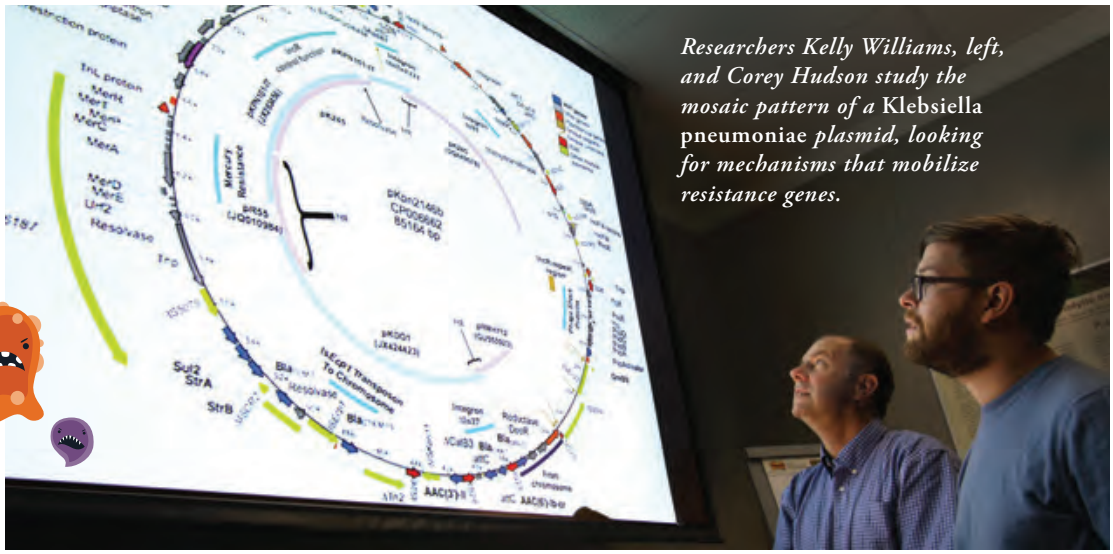
Sandia Labs microbiologists studying infectious diseases sequenced in 2014, for the first time, the whole genome of a *Klebsiella pneumoniae* strain that encodes New Delhi metallo-beta-lactamase (NDM-1). This enzyme makes the strain resistant to carbapenems, the antibiotics of last resort. *K. pneumoniae* is the most common species of carbapenem-resistant Enterobacteriaceae (CRE) in the United States

These opportunistic bacteria can grow on hospital surfaces or in lungs and tissues, and can spread their resistance to other bacteria. According to the Centers for Disease Control and Prevention, about one in 25 hospital patients has an antibiotic-resistant infection, lethal in up to one in nine cases.

K. pneumoniae strains are known for "their ability to survive any antibiotics you throw at them," says Corey Hudson. He, Robert Meagher and Kelly Williams, along with former postdoctoral employee Zach Bent, made valuable use of Sandia's new genome sequencing capabilities to identify several mechanisms bacteria use to share genes to expand their repertoire of antibiotic resistance. In some cases, bacteria can receive a new set of genes all at once and in the process become pathogenic.

The team is now focused on mechanisms involving genomic islands — mobile DNAs that can splice themselves into bacterial chromosomes. Genomic islands carry genes that contribute to everything from metabolism to pathogenicity, and move clusters of genes all at once between species. They, along with circular plasmids residing in the cells and bacterial viruses, are the major mechanism for evolution in organisms that lack a true nucleus.

By Sue Major Holmes



Researchers Kelly Williams, left, and Corey Hudson study the mosaic pattern of a Klebsiella pneumoniae *plasmid, looking for mechanisms that mobilize resistance genes.*

Understanding how genomic islands move and their effect on bacterial physiology could lead to new approaches to bypass bacterial defenses, Hudson says. Bacteria share genetic material through free virus particles or through a cell-to-cell process called conjugation. One bacterium sends out a tube from its surface into another's, and injects genes into the other cell, Williams says.

A hypothetical example of sharing: A local water supply is contaminated with a pathogenic *E. coli* strain that is not antibiotic-resistant. *K. pneumoniae* enters the water, comes into contact with the *E. coli,* and donates genes. Now a pathogenic *E. coli* has acquired resistance, making it harder to eradicate. "The great challenge is that bacteria can easily share their defense," Williams says.

Over the two decades that bacterial genomes have been sequenced, researchers have found that bacteria share genes rampantly. "They are not so much generating new genes all the time — that does happen slowly — but what they mainly do is shuffle genes around," Williams says. "The new gene combinations can quickly give bacteria a new pathogenic niche. They may then invade more tissues or survive even more conditions."

Since publishing the genomic analysis, Sandia's project has developed an experimental technique that detects genomic islands on the move. The team applies a computational or bioinformatics technique to identify islands in genomes and performs "transcriptomic" studies of gene expression to see which antibiotic-resistance and other genes get turned on during an infection.

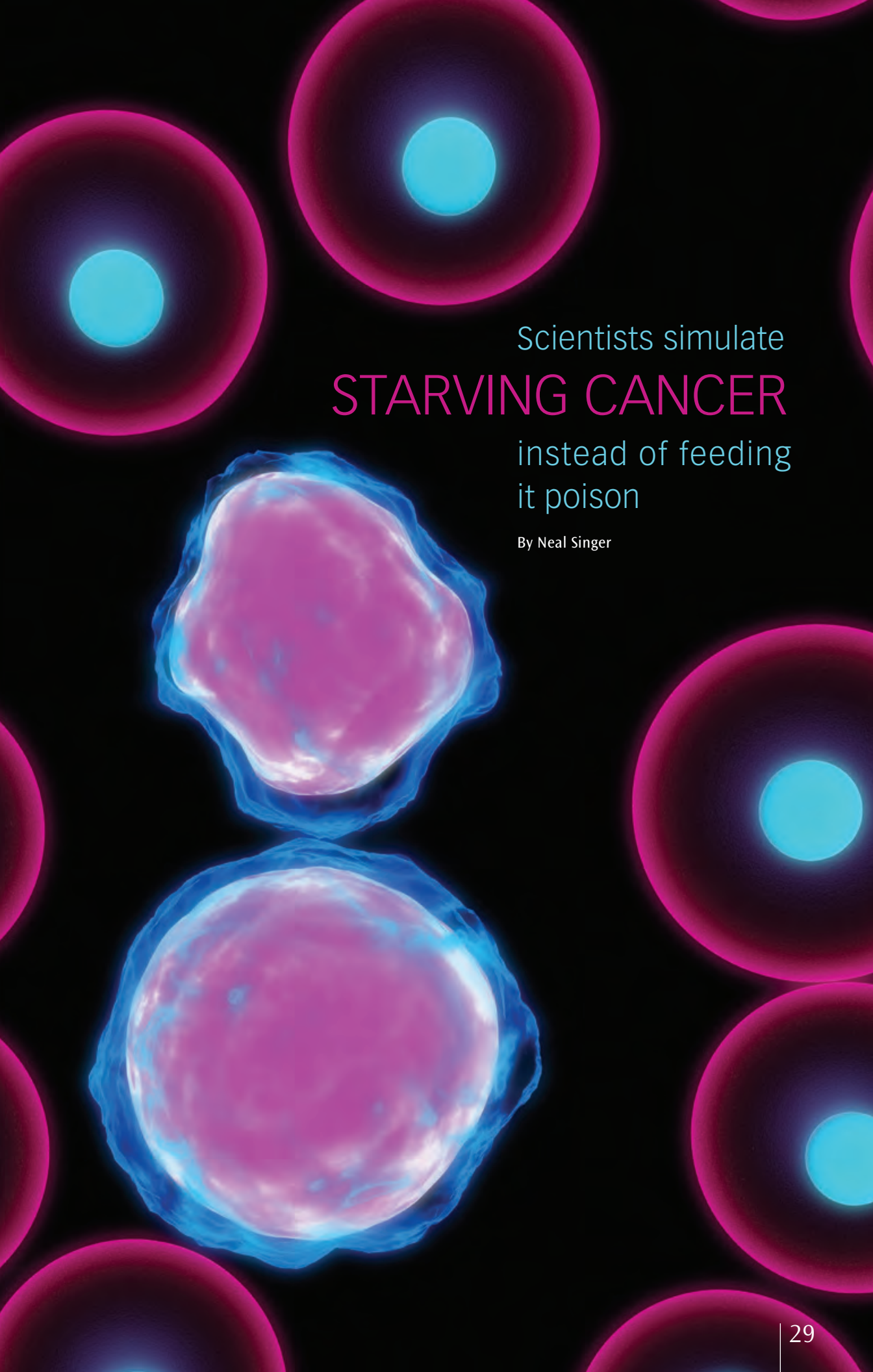
The research showed the beta-lactamase genes in *K. pneumoniae* were on all the time, whether the bacteria were infecting human cell cultures or not. In essence, Williams says, "the bug is always armed" against antibiotics.

The team built a database of genomic islands they found in a survey of all sequenced bacteria. As of early 2015, the database contained nearly 4,000 genomic islands, which is a partial list of what bacteria share, Hudson says. The database reveals both global features of genomic islands and unique features in select groups of bacteria.

Rather than relying solely on bioinformatics, the team invented a new experimental approach to detect islands as they pop out of the genome. The team stimulates this beginning stage of island mobilization by stressing the cells in certain ways. In this stage the island takes a circular form, free of the chromosome, but has not yet moved to another cell.

Experiments and bioinformatics work together, each yielding information the other did not and confirming each other. "We do what we can with the computer, but we like to test the resulting hypotheses in the lab," Williams says.

Eventually, the work might lead to a way to predict new pathogens before they emerge as public health threats. "We're just starting on this path," Williams says. "It's a harder problem to predict emerging pathogens, rather than just observe them. Determining what is pathogenic in the first place and how it might become more pathogenic is a research challenge." ■



Scientists simulate STARVING CANCER instead of feeding it poison

By Neal Singer

Treatment offers hope of killing a growth without sickening the patient

A patent application for a drug that could destroy the deadly childhood cancer acute lymphoblastic leukemia — and potentially others — has been submitted by researchers at Sandia Labs, the University of Maryland and the MD Anderson Cancer Center in Houston.

Susan Rempe says a new approach to treating cancer is being tested on laboratory mice. If successful, human testing will follow.

"Most drugs have to go inside a cell to kill it," says Sandia researcher Susan Rempe. "Our method withholds an essential nutrient from the cell, essentially starving it until it self-destructs." The removed nutrient is asparagine, which the bad cells can't produce on their own. But there's more to the story.

It's well-known that chemical cancer treatments often sicken the patient. In the case of the cancer drug L-asparaginase, which depletes asparagine, side effects can be caused by the corresponding depletion of the chemically similar molecule glutamine. All human cells need asparagine and glutamine to survive because each is essential to key biological processes. While normal cells can synthesize their own asparagine, certain cancer cells cannot. So the ideal nutrient-deprivation strategy requires a difficult balancing act: Remove enough asparagine from the blood to cripple the cancer, but leave enough glutamine that the patient can tolerate chemotherapy.

The Sandia and Maryland researchers did molecular simulations to predict which mutations would produce that result when introduced into the enzyme drug L-ASN2, commonly used to treat certain types of leukemia. The scientists' simulations identified a point in the enzyme's chain of amino acids where a mutation theoretically would thwart the drug's attack on glutamine.

"Technically," says Rempe, "we simulated which parts of the two molecules came in contact with the enzyme. Then we realized that by substituting a single amino acid in the enzyme's chain, we might avoid glutamine degradation by removing it from contact with the enzyme."

The technique looked promising in computer simulations because the most notable difference between asparagine and glutamine was the way

they interacted with that particular amino acid. "That made us feel that a chemical change at that one location was the key," says Rempe.

It required a mutation to change the amino acid's chemistry. Collaborators at MD Anderson used DNA substitutions to effect the change. "Most researchers agree that removing glutamine from a patient's blood was the problem in previous use of this enzyme drug," says Rempe. "Our simulations showed how to avoid that."

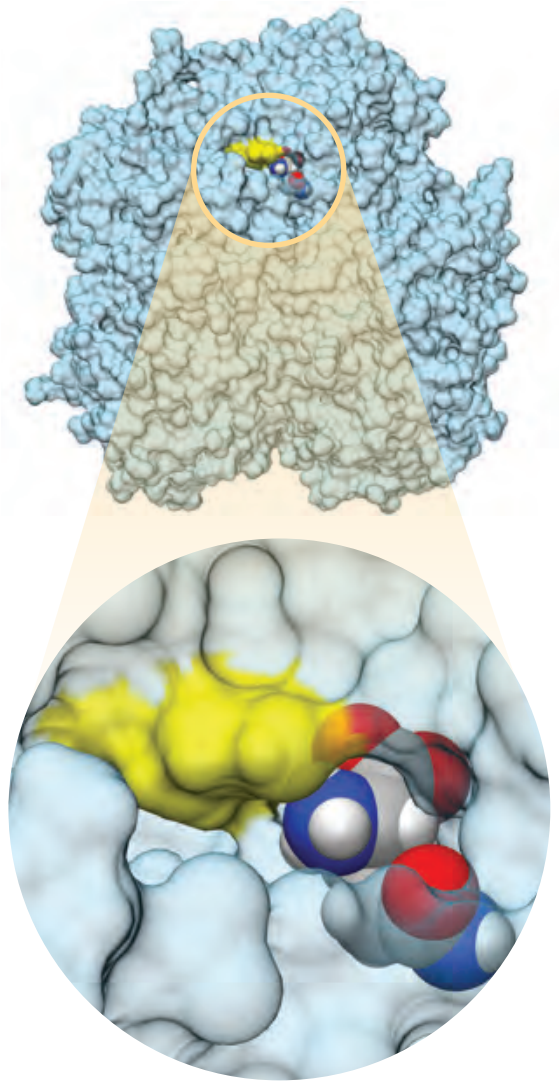
The new drug left glutamine untouched in test tube experiments. Follow-up tests in petri dishes showed the mutated enzyme killed a variety of cancers. Tests on laboratory rats at MD Anderson should be completed by early 2016 and, if successful, human testing will follow, Rempe says. "If we're wrong, and keeping glutamine intact is not the answer to the cancer problem, we'll continue investigating because we think we're onto something," she says.

That's because, she says, "we used high-resolution computational methods to redesign the cancer drug to act differently, in this case to act only on asparagine. Laboratory tests showed that the predictions worked and that the new drug kills a variety of leukemias. We hope our method can do that in a patient, and for many more cancers. But if it doesn't, then we'll test the opposite strategy: redesign the enzyme to destroy glutamine and keep asparagine intact. We're learning to control this enzyme."

The collaboration between Sandia, the University of Maryland and MD Anderson began in 2009. Sandia managers Wahid Hermina and Steve Casalnuovo spearheaded the effort to use computational and biochemical expertise developed in national defense to help in the fight against cancer.

Sandia's cancer-fighting research also can be applied to building enzymes that can help with biodefense. "If we could redesign an enzyme to break down specific small molecules, and not get diverted by interactions with nontoxic molecules, then we could apply our technique to develop safer and more effective enzymes," Rempe says.

Classical modeling was performed at the University of Maryland by Andriy Anishkin and Sergei Sukharev; at Sandia, postdoctoral researcher David Rogers (now at the University of South Florida) also did modeling studies. Sandia postdoctoral researcher Juan Vanegas is performing quantum modeling to map out the chemical degradation process to better understand how to optimize the enzyme, Rempe says. The experiments at MD Anderson were done by Phil Lorenzi, John Weinstein and colleagues. Results have been published in the journal *Blood*.



A simulation by researchers at Sandia Labs and the University of Maryland demonstrates that a mutated enzyme, in yellow, will degrade asparagine — food for some cancers — but leave glutamine, necessary for all proteins, untouched. (Graphic by Juan Vanegas)

The work is supported in part by Sandia's Laboratory Directed Research and Development program. ■

Sandia
RESEARCH

Sandia National Laboratories
P.O. Box 5800, MS 0359
Albuquerque, NM 87185-0359

LOOKING BACK

A MICRO DEVICE THAT IS ANYTHING BUT SMALL

It was compact and light enough to fit in a hand. It harnessed the power of a full chemistry laboratory, detecting and analyzing toxic agents such as bacteria, viruses and protozoa in minutes rather than hours. And it did its work using only minuscule amounts of sample and analytes.

Introduced during the heyday of the late 1990s biotech boom, Sandia's µChemLab sparked major excitement at scientific conferences worldwide.

The micro device, created out of Sandia's first Grand Challenge Laboratory Directed Research and Development project, was a milestone on a strategic path to establish the lab as a microfluidics authority. Grand Challenges pursue high-risk ideas with significant potential for national impact.

Sandia has enhanced the basic technology behind µChemLab, generated a multitude of patents and garnered national recognition, most recently a 2012 R&D 100 award for an entire integrated system for automated sample preparation and analysis of micro-liter volumes.

Since 2000, Sandia has attracted top minds and hundreds of millions of sponsorship dollars from several agencies to explore the value of the technology in an array of contexts, from addressing chemical and biological threats to rapidly diagnosing disease.

Industry has taken note, joining Sandia in cooperative research and development agreements, some leading to commercial products. And proving that innovation breeds innovation, the µChemLab has spurred a half dozen startup companies and unanticipated uses such as monitoring for gases released during fracking.

More than a decade after the first prototype was launched, the momentum remains strong as Sandia continues to receive funding for new applications of the microfluidics technology in national security, public health and energy.

— Holly Larsen

The three principal components of Sandia's µChemLab are small enough to fit inside a snow-pea pod.